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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,824	07/14/2003	Lieping Chen	07039-427001 / MMV-02-228	7199

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/619,824	CHEN ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 – 3, 5, 7 – 8, 10 – 13, 17 – 18, 20, 23 and 26 – 31* is/are pending in the application.

4a) Of the above claim(s) *11 - 13 and 29 - 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 – 3, 5, 7 – 8, 10, 17 – 18, 20, 23, and 26 – 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/24/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed on 03/24/2008 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/24/2008 has been entered.

Claims 4, 6, 9, 14 – 16, 19, 21 – 22, 24 – 25, and 32 – 34 have been canceled.

Claims 1 – 3, 5, 7 – 8, 10 – 13, 17 – 18, 20, 23, and 26 – 31 are pending.

Claims 11 – 13 and 29 – 31 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Inventions/Species, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 03/27/2006.

Claims 1 – 3, 5, 7 – 8, 10, 17 – 18, 20, 23, and 26 – 28 are under consideration in the instant application, as they read on the elected invention drawn to methods wherein the subject has systemic lupus erythematosus.

The rejections of record can be found in the previous Office Action, mailed on 02/22/2007.

The rejections of record have been withdrawn in view of Applicant's amendment and arguments, except as set forth herein.

It is noted that New Grounds of Rejection are set forth herein.

2. The following is a quotation of the **first paragraph of 35 U.S.C. 112**:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1 – 3, 5, 7 – 8, and 10 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for decreasing the number of $CD4^+$ T cells and increasing the number of $CD8^+$ T cells in a subject by administering an antibody that binds to 4-1BB, does not reasonably provide enablement for a method for treating or preventing an autoimmune disease, a lymphoproliferative disease, or an allergy by administering an antibody that binds to 4-1BB. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to make and use the invention as claimed without undue experimentation. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The instant specification discloses in Examples 3 – 6 that administration of anti-4-1BB antibody 2A ameliorates various manifestations of disease in MRL/lpr mice, a strain which spontaneously develops lupus-like symptoms due to a mutation affecting expression of Fas, an apoptotic regulator. However, one of skill in the art is aware that

systemic lupus erythematosus (SLE) in humans is a heterogeneous multi-factorial disease, believed to be caused by an interaction of environmental stimuli with multiple small genetic differences (as reviewed e.g. by Merrill J.T., Expert Opin. Emerging Drugs, 2005, 10: 53 – 65; see entire document, in particular, e.g. Figure 1 and pages 61 – 62). Therefore, the results based on manipulation of 4-1BB pathway in Fas-deficient mice cannot be seen as predictive of human clinical outcomes in SLE, or in general in autoimmune disease, lymphoproliferative disease, or allergy, as generically claimed.

Furthermore, one of skill in the art is aware that the efficacy of therapeutic antibodies can be species- and model-dependent, and therefore it is unpredictable whether reliance on the experimental observations in the experimental model described in the instant specification provide the basis for employing the recited antibodies for treating any of the recited diseases. For example, Blazar et al. (J. Immunol., 1996, 157: 3250 – 3259; see entire document, in particular, e.g. page 3257, column 2 first paragraph) disclose that issues such as tissue distribution, half-life, affinity and avidity obtained with various reagents targeting T cell costimulatory molecules might prove to be highly important in achieving a therapeutic effect. Therefore, any conclusion regarding the efficacy of costimulatory modulation on altering in vivo immune response should be interpreted in light of the specific reagent used (Blazar et al., see page 3257, column 2, paragraph 1). Thus there is no evidence that the animal model used in the experiments disclosed in the specification would be predictive of the therapeutic methods encompassed by the claims.

Pharmaceutical therapies using biomolecules are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as

adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Further, the burden of enabling the prevention of a disease (i.e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to the recited diseases within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently methods in preventing these disease states. Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention for preventing a disease.

In view of insufficient guidance by the instant specification and the lack of predictability of the art to which the invention pertains with respect to the 4-1BB signaling pathway, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of the clinical protocols, and absent working examples providing evidence that the claimed methods are effective for treating any autoimmune or lymphoproliferative diseases other than the experimental disease in MRL/lpr mice.

4. The following is a quotation of the appropriate paragraphs of **35 U.S.C. 102** that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1 – 3, 5, 7 – 8, 10, 17 – 18, 20, 23, and 26 – 28 stand rejected under **35 U.S.C. 102(b)** as being anticipated by Kang et al. (US Patent No. 5,928,893; of record), for the reasons of record.

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that Kang et al. fail to teach the specific type of antibody required by the instant claims, or which cells are suppressed.

In response, the method Kang et al. comprises administering antibodies specific for the same protein as instantly recited, to the same patient population as instantly recited. Therefore, the mechanism of action of the antibodies is inherently the same as instantly recited, regardless of whether Kang et al. were aware of those mechanisms. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Furthermore, the instantly recited and referenced antibodies appear to have equivalent binding specificities. The Office is not in a position to test the antibody described in the prior art for the functional properties recited in the instant claims. The burden is on the applicant to establish a patentable distinction between the claimed and referenced antibodies. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

Therefore, the rejection of record is maintained for the reasons of record, as it applies to the amended claims. The rejection or record is incorporated by reference herein, as if reiterated in full.

6. Claims 1 – 3, 5, 7 – 8, 10, 17 – 18, 20, 23, and 26 – 28 stand rejected under **35 U.S.C. 102(a) and 102(e)** as being anticipated by B. Kwon (US Patent No. 6,303,121; of record), for the reasons of record.

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that the fact that two antibodies bind to the same target does not necessarily mean that both antibodies will have the same effect.

This is not found persuasive, because, given that the antibody in the prior art is administered for the same condition as instantly recited, it must necessarily have the same effect as instantly recited.

Furthermore, the Office is not in a position to test the antibody described in the prior art for the functional properties recited in the instant claims. The burden is on the applicant to establish a patentable distinction between the claimed and referenced

antibodies. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

Therefore, the rejection of record is maintained for the reasons of record, as it applies to the amended claims. The rejection or record is incorporated by reference herein, as if reiterated in full.

7. Conclusion: no claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is (571)272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ILIA OUSPENSKI, Ph.D./
Primary Examiner, Art Unit 1644
May 7, 2008